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Severity of depression in abstinent alcoholics is associated with monoamine metabolites and dehydroepiandrosterone-sulfate concentrations

Andreas Heinz[a,b,*], Herbert Weingartner[a], David George[a], Daniel Hommer[a], Owen M. Wolkowitz[c], Markku Linnoila[a]

[a] *National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD 20892, USA*
[b] *Central Institute of Mental Health, University of Heidelberg, 68159 Mannheim, Germany*
[c] *University of California, San Francisco, CA 49143, USA*

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Abstract

Depressed mood increases the relapse risk of abstinent alcoholics; its neurobiological correlates may include reduced serotonin and norepinephrine turnover rates and increased cortisol concentrations during detoxification stress. Neurosteroids such as dehydroepiandrosterone and its sulfate (DHEA and DHEA-S) may antagonize cortisol action and may have mood-elevating effects on their own. We measured severity of depression with Beck's Depression Inventory (BDI) and Hamilton's Depression Rating Scale (HDRS), plasma concentrations of cortisol, DHEA and DHEA-S, and CSF concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and the dopamine metabolite homovanillic acid (HVA) in 21 abstinent alcoholics after 4 weeks of abstinence and in 11 age-matched healthy control subjects. Only CSF MHPG concentrations were reduced in alcoholics compared to control subjects (41.4 ± 6.6 vs. 53.3 ± 8.6 pmol/ml). Self-rated depression was significantly correlated with CSF MHPG (Spearman's $R = +0.57$, $P < 0.01$), CSF 5-HIAA ($R = +0.51$, $P < 0.05$) and plasma cortisol concentrations ($R = +0.50$, $P < 0.05$). Negative correlations were found between DHEA-S concentrations and both self-rated depression ($R = -0.45$, $P < 0.05$) and observer-rated depression ($R = -0.55$, $P < 0.05$). The ratio of DHEA-S to cortisol serum concentrations was also negatively correlated with depression (BDI: $R = -0.55$, $P < 0.01$; HDRS: $R = -0.63$, $P < 0.005$). Anxiety (Spielberger's State Anxiety Scale) was only associated with CSF MHPG concentrations ($R = +0.58$, $P < 0.01$). Our findings point to the

* Corresponding author. Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, University of Heidelberg, J5, 68159 Mannheim, Germany. Tel.: +49-621-1703-721; fax: +49-621-1703-945.
E-mail address: heinza@as200.zi-mannheim.de (A. Heinz)

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importance of noradrenergic dysfunction in the pathogenesis of depression among abstinent alcoholics and indicate that their mood states may also be modulated by a low DHEA-S to cortisol ratio, hypothetically indicative of low stress protection capacities.

Keywords: Depression; Alcoholism; Neurosteroids; Detoxification stress; Cortisol; DHEA-S

1. Introduction

Among alcoholics, persistence of depressed mood after detoxification is associated with a long-term increase in the relapse risk (Hartka et al., 1991; Wagner Glenn and Parsons, 1991). The neurobiological correlates of depression among abstinent alcoholics may include hormonal and neurotransmitter pathways that are also implicated in the pathogenesis of major depression. In major depression, widespread evidence points to a pathogenic role of central monoaminergic dysfunction (Van Praag, 1977; Kraemer and McKinney, 1979; Delgado et al., 1993; Young et al., 1994) and an increased activation of the hypothalamic–pituitary–cortisol axis (Dinan, 1994). Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are neurosteroids that modulate the NMDA and $GABA_A$ receptor (Randall et al., 1995; Baulieu, 1997) and that may interact with central serotonergic neurotransmission (Abadie et al., 1993). DHEA may also potentiate the release of the monoamine norepinephrine (Monnet et al., 1995). Many (Osran et al., 1993; Ferguson et al., 1964; Legrain et al., 1995; Berr et al., 1996; Goodyer et al., 1996; Herbert 1998), but not all (Tollefsen et al., 1990; Heuser et al., 1998) studies have found decreased levels of DHEA(S) or decreased ratios of DHEA(S) to cortisol in depressed patients. In any event, DHEA application has been shown to alleviate depression in patients with major depression and dysthymia (Wolkowitz et al., 1997, 1999; Bloch et al., 1999). Basal DHEA and DHEA-S concentrations did not differ significantly between alcoholics and control subjects (Adinoff et al., 1996a). However, these neurosteroids were found to be reduced under conditions of severe stress or corticosteroid treatment (Parker, 1989; Guazzo et al., 1996). Cortisol concentrations are known to be increased during early detoxification (Iranmanesh et al., 1989; Von Bardeleben et al., 1989; Heinz et al., 1995a) and may also interact with serotonin turnover (Meltzer et al., 1994). Among abstinent alcoholics, dysfunction of serotonin turnover and uptake has been observed and may affect mood states (Ballenger et al., 1979; Fils-Aime et al., 1996; Heinz et al., 1998).

To assess the interaction between depression and stress hormones, neuromodulators and central serotonergic neurotransmission in abstinent alcoholics, we measured plasma cortisol, DHEA and DHEA-S concentrations and concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF). Some authors have suggested that DHEA and its sulfate antagonize certain effects of cortisol (Browne et al., 1992; Kalimi et al., 1994) and that examination of the ratios of DHEA and DHEA-S to cortisol may be more informative than examination of individual hormone levels (Fava et al., 1989; Wolkowitz et al., 1997). Therefore we also assessed the correlations between severity of depression and both DHEA/cortisol and DHEA-S/cortisol concentrations. We hypothesized that severity of depression among abstinent alcoholics would be associated with increased cortisol concentrations, decreased concentrations of DHEA and DHEA-S and their respective ratios to cortisol, and reduced CSF 5-HIAA concentrations.

2. Methods

2.1. Subjects and assessment of severity of depression

All subjects provided written informed consent for this study under protocols approved by the Institutional Review Boards of the Intramural

Research Program of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Six female and 15 male patients participated in the study; all patients had abstained from alcohol for 4 weeks and fulfilled criteria for alcohol dependence according to DSM-III-R criteria. Exclusion criteria were current drug abuse (a positive urine drug screen) or a past history of drug dependence other than alcoholism, serious head trauma, or the presence of psychiatric (axis I diagnosis) and neurological disorders unrelated to alcoholism (SCID I; Spitzer et al., 1990a). Patients were withdrawn from alcohol as inpatients in the Intramural Research Program of the NIAAA. Blood and CSF samples were acquired after 4 weeks of supervised abstinence (random breath testing). Given the strong effect of duration of abstinence on monoaminergic neurotransmission (Heinz et al., 1995b, 1998; Laine et al., 1999), we assessed alcoholics after 4 weeks of abstinence and were therefore not able to match female alcoholics for menstrual cycle phase. Patients did not receive any psychotropic or antiepileptic medication, steroids or methyldopa in the 3 weeks prior to laboratory assessment. Fourteen alcohol-dependent patients and one control subject smoked.

Four age-matched women and seven men served as healthy volunteer subjects (Table 1). They did not have any axis I diagnoses or personality disorders according to DSM-III-R (SCID I and SCID II; Spitzer et al., 1990a,b) and had no alcohol-dependent first degree relatives. We used the extended version of the Michigan Alcohol Screening Tool (Selzer, 1971; Fils-Aime et al., 1996) which includes a detailed assessment of previous drug consumption to assess prior substance abuse or dependence in both control subjects and patients. To verify the statements on drug and alcohol abuse, random urine and breath testing was carried out.

Depression was rated weekly during the first 4 weeks of abstinence using Beck's Depression Inventory (BDI; Beck et al., 1961) and the 21-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). At this time, anxiety levels were measured with Spielberger's State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970), and education and social status were assessed with Hollingshead's Four Factor Index of Social Skills (Hollingshead, 1973).

Table 1
Clinical data of healthy control subjects and alcohol-dependent patients[a]

	Healthy control subjects	Alcoholics
Age (years)	40 ± 11	38 ± 7
Sex	4 females, 7 males	6 females, 15 males
Lifetime absolute alcohol consumption (kg)	17 ± 19	651 ± 710*
Absolute alcohol consumption in the last 6 months (kg)	0.5 ± 1.0	21.2 ± 14.2*
Education (Hollingshead Scale score)	6.3 ± 0.7	5.3 ± 1.2*
Social status (Hollingshead Scale score)	7.1 ± 1.2	6.3 ± 1.9*
MCV (μm^3)	87 ± 6	100 ± 8
Albumin (g/dl)	4.6 ± 0.3	4.6 ± 0.3
S-ALT (units/l)	21 ± 6	53 ± 40*
S-AST (units/l)	21 ± 5	63 ± 53*
G-GTP (units/l)	21 ± 9	141 ± 139*
Cortisol (μg/dl)	11.5 ± 3.1	13.3 ± 3.9
DHEA (ng/dl)	405 ± 196	516 ± 224
DHEA-S (μg/ml)	1.9 ± 1.2	2.0 ± 0.9
5-HIAA (pmol/ml)	66.5 ± 18.5	76.9 ± 21.5
MHPG (pmol/ml)	53.3 ± 8.6	41.4 ± 6.6**
HVA (pmol/ml)	176.8 ± 50.1	146.4 ± 60.7
Beck's Depression Inventory	1.9 ± 3.7	7.0 ± 5.6**
Hamilton Depression Rating Scale	1.9 ± 3.5	7.7 ± 5.1***
Spielberger's State-Trait Anxiety Inventory	29.3 ± 10.9	43.7 ± 6.8*

[a] Student's t-test: $*P < 0.05$; $**P < 0.001$; $***P < 0.0001$.

2.2. Procedures for obtaining blood and CSF samples

Subjects were on a low monoamine diet for 3 days prior to both blood withdrawal and lumbar puncture (LP). Blood and CSF samples were acquired after overnight bed rest and fast. CSF samples were not available in female control subjects and DHEA/DHEA-S values were missing in two male alcoholics. Serum DHEA, DHEA-S

and cortisol concentrations were checked after 4 weeks of abstinence at 08.00 h. An intravenous catheter was inserted and flushed with 0.9% NaCl; subjects rested flat in bed and, 30 min later, blood samples were obtained for hormonal assessments. To obtain CSF samples, LP was performed in the same week as the hormonal assessment between 09.00 and 10.00 h. Among healthy volunteers, CSF samples were available only in the male subjects. The first 12 ml of CSF were collected as a single aliquot into a tube on wet ice. After the LP, that CSF was mixed and aliquoted into several 1- and 2-cm^3 tubes, which were stored immediately at $-80°C$. None of the samples were thawed before analysis.

2.3. Laboratory assessments

DHEA was assayed by charcoal separation and ^{3}H-radioimmunoassay (DSL, Webster, TX, USA), DHEA-S by double-antibody, ^{125}I-based radioimmunoassay (ICN Biomedicals Inc., Diagnostic Division, Costa Mesa, CA, USA). Serum cortisol was analyzed using the Abbott Tdx analyzer (Abbott Laboratories, Abbott Park, IL, USA) which uses a fluorescence polarization method. All samples were run in duplicate in the same assay; at least two levels of quality control pools were run in each of the two assays. For serum cortisol, evaluation of precision over 20 days showed a coefficient of variation (CV) of 5.2% at a level of 10 μg/dl and 4.1% at a level of 48 μg/dl. Within-run precision for 20 repeats was 3.0% at 10 μg/dl and 2.1% at a level of 47 μg/dl. For DHEA, the intra-assay CV was 6.7% at a level of 150 ng/dl and 5.4% at a level of 834 ng/dl; the inter-assay CV was 6.5% at a level of 150 ng/dl and a 6.6% at a level of 834 ng/dl. For DHEA-S, the intra-assay CV was 6.6% at a level of 1.98 μg/ml and 6.0% at a level of 5.68 μg/ml; the inter-assay CV was 8.5% at a level of 2.15 μg/ml and 9% at a level of 7.96 μg/ml. Under the assay conditions used, DHEA antibody had a cross-reactivity with DHEA-S of 0.02%.

To assess central monoamine metabolism, concentrations of CSF 5-HIAA, HVA and MHPG were determined with high-pressure liquid chromatography (Scheinin et al., 1983; Virkunnen et al., 1994); every individual sample was duplicated in each of the two runs. Internal standards of MHPG-hemipiperazinium salt, HVA and 5-HIAA were purchased from Sigma (St. Louis, MO, USA). F-HVA was a gift from Kenneth Kirk (NIDDK, Bethesda, MD, USA). The intra-day variation for each compound was less than 3%; the inter-day variation less than 5%.

2.4. Statistical analysis

Group differences between healthy control subjects and alcoholics were assessed using Student's *t*-test. Correlations between mood states and neurobiological variables were assessed using Spearman's linear correlation coefficient.

To account for potential gender differences in the assessed neurobiological and psychopathological variables (Yamaji and Ibayashi, 1969; Orentreich et al., 1984), we compared male and female alcoholics and control subjects with an ANOVA followed by Tukey's Honest Significant Differences Test (TSD). Furthermore, we separately assessed correlations between mood states and cortisol, neuromodulators and CSF 5-HIAA among the 15 male alcoholics (the number of six female alcoholics was too small for meaningful separate correlations). To control for unspecific effects on severity of depression, we evaluated effects of body mass index, socioeconomic status, smoking and age (Orentreich et al., 1984).

3. Results

Severity of depression among alcoholics was highest during detoxification and decreased significantly during the first 2 weeks of abstinence (BDI: 17 ± 9 vs. 8 ± 6; HDRS: 18 ± 8 vs. 8 ± 6). Afterwards, mood states remained stable during the observation period. After 4 weeks of detoxification, depression and anxiety were significantly increased among abstinent alcoholics compared to control subjects (Tables 1 and 2). CSF MHPG was significantly decreased in male and female alcoholics compared to male control subjects

Table 2
Cortisol, DHEA, DHEA-S and CSF 5-HIAA, MHPG and HVA in alcoholics and control subjects

	Male control subjects	Female control subjects	Male alcoholics	Female alcoholics
Number	$n = 7$	$n = 4$	$n = 15$	$n = 6$
Age (years)	42 ± 12	34 ± 6	39 ± 6	37 ± 7
Age of onset (years)	–	–	24 ± 6	25 ± 5
Cortisol (μg/dl)	12.09 ± 1.59	10.26 ± 5.69	14.09 ± 4.12	11.97 ± 3.20
DHEA (ng/dl)	314 ± 137	542 ± 205	567 ± 216	387 ± 203
DHEA-S (μg/ml)	1.67 ± 0.98	2.23 ± 1.67	2.24 ± 0.78	1.28 ± 0.91
CSF 5-HIAA (pmol/ml)	66.5 ± 18.5	not available	71.16 ± 16.90	90.86 ± 26.12
CSF MHPG (pmol/ml)	53.3 ± 8.6	not available	42.0 ± 6.5*	39.9 ± 7.1*
CSF HVA (pmol/ml)	176.8 ± 50.1	not available	131.4 ± 41.4	182.9 ± 85.8
Beck's Depression Inventory	2 ± 4	1 ± 3	7 ± 6*	6 ± 3*
Hamilton Depression Rating Scale	2 ± 4	1 ± 3	7 ± 5*	10 ± 6*
Spielberger's State-Trait Anxiety Inventory	24 ± 6	34 ± 14	44 ± 12	43 ± 14

*$P < 0.05$ vs. healthy control subjects (ANOVA plus TSD).

(ANOVA, $F = 7.74$, d.f. = 2, $P < 0.005$; TSD < 0.05 for both male and female alcoholics). No significant differences in serum cortisol, DHEA(S) and DHEA(S)/cortisol concentrations or in CSF 5-HIAA or HVA concentrations were found between patients and control subjects (Tables 1 and 2).

Among alcoholics, serum cortisol concentrations were significantly correlated with self-rated ($R = +0.50$, $P < 0.05$) but not observer-rated depression (Table 3). DHEA-S and DHEA-S/cortisol concentrations were associated with severity of both self-rated and observer-rated depression (BDI vs. DHEA-S: $R = -0.45$, $P < 0.05$; HDRS vs. DHEA-S: $R = -0.55$, $P < 0.05$; BDI vs. DHEA-S/cortisol: $R = -0.55$, $P < 0.01$; HDRS vs. DHEA-S/cortisol: $R = -0.63$, $P < 0.005$) (Fig. 1). No significant correlations between mood states and DHEA or CSF HVA concentrations were observed. A significant correlation was found between both CSF 5-HIAA and MHPG concentrations and severity of self-rated depression (CSF 5-HIAA vs. BDI: $R = +0.51$, $P < 0.05$; CSF MHPG vs. BDI: $R = +0.57$, $P < 0.01$); the correlations with observer-rated depression failed to reach statistical significance (Table 3). Anxiety significantly correlated with CSF MHPG concentrations ($R = +0.58$, $P < 0.01$), but not with cortisol, DHEA-S, DHEA, DHEA-S/cortisol, CSF 5-HIAA or HVA concentrations. Concentrations of 5-HIAA and HVA were significantly correlated ($R = +0.70$, $P < 0.001$); no significant correlations were observed between the other assessed neurobiological variables.

When male alcoholics were assessed separately, all significant correlations in Table 2 remained in a similar range with the exception of the correlation between DHEA-S/cortisol and HDRS, which no longer reached statistical significance ($R = -0.36$, $P = 0.17$); conversely, the correlation between CSF 5-HIAA and HDRS now approached statistical significance ($R = +0.52$, $P = 0.05$).

Age was negatively correlated with concentrations of DHEA and DHEA-S ($R = -0.50$ and $R = -0.52$, $P < 0.05$), but not with cortisol or CSF monoamine concentrations. A stepwise multiple regression analysis was performed to assess the interaction between severity of depression and age, cortisol, DHEA-S, CSF 5-HIAA and CSF MHPG concentrations. Cortisol concentrations emerged as the only factor which was significantly associated with self-rated depression (BDI: $\beta = 0.79$, $R^2 = 0.49$, $P < 0.05$), while

Table 3
Correlations between neurobiological variables and severity of self- (BDI) and observer-rated depression (HDRS) and anxiety (STAI) among abstinent alcoholics[a]

	BDI	HDRS	STAI
Cortisol	+0.50*	+0.20	+0.39
DHEA-S	−0.45*	−0.55*	−0.08
DHEA-S/Cortisol	−0.55**	−0.63***	−0.23
DHEA	+0.01	−0.27	+0.10
5-HIAA in CSF	+0.51*	+0.38	+0.25
MHPG in CSF	+0.57**	+0.18	+0.58**
HVA in CSF	+0.23	+0.08	−0.01

[a]Spearman's R: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.005$.

DHEA-S concentrations approached a significant interaction with observer-rated depression (HDRS: $\beta = -0.54$, $R^2 = 0.33$, $P = 0.05$).

Severity of depression or anxiety was not associated with age, body mass index, education or social status; male and female alcoholics did not significantly differ in these variables or in severity of depression. Liver function tests were not associated with neurosteroid concentrations. Smokers did not differ from non-smokers in the assessed neurobiological or psychopathological variables; this was also true when we compared only smoking and non-smoking alcoholics.

4. Discussion

Severity of depression in abstinent alcoholics was associated with concentrations of cortisol and DHEA-S in plasma, and with concentrations of

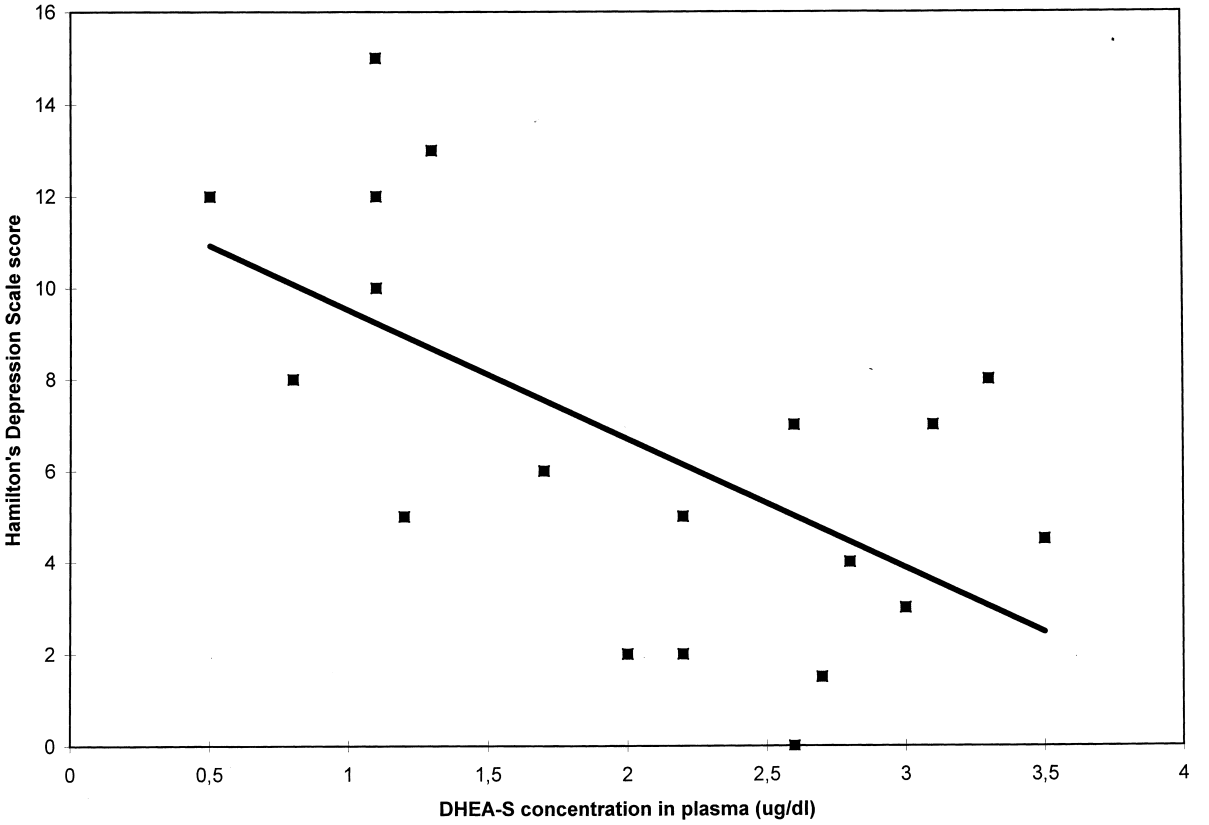

Fig. 1. Correlation between DHEA-S serum concentrations and the severity of depression (Hamilton's Depression Rating Scale) in 19 abstinent alcoholics (Spearman's $R = -0.55$, $P < 0.05$).

the serotonin metabolite 5-HIAA and the norepinephrine metabolite MHPG in CSF. Of these variables, only CSF MHPG concentrations were reduced in alcoholics compared with control subjects. In the absence of group differences between alcoholics and control subjects, the correlations between severity of depression and DHEA-S, cortisol and CSF 5-HIAA concentrations among the alcoholics may indicate that neurosteroids and CSF 5-HIAA modulate severity of depression in alcoholics, which is caused by some other, undetected factors. Based on studies showing that norepinephrine depletion may cause depression (Kraemer and McKinney, 1979; Delgado et al., 1993), it is tempting to speculate that reduced CSF MHPG concentrations are one of the factors directly involved in the pathogenesis of negative mood states in alcoholics. However, both severity of depression and CSF MHPG concentrations are known to decrease during the first weeks of abstinence, arguing against a simple causation of depression by reduced noradrenergic neurotransmission (Borg et al., 1983; Hawley et al., 1994).

The positive correlation between severity of self-rated depression and CSF MHPG and 5-HIAA concentrations was unexpected, as antidepressant medication is known to acutely increase synaptic monoamine concentrations (Delgado et al., 1993; Owens and Nemeroff, 1994). However, chronic application of selective serotonin reuptake inhibitors and tricyclics was associated with reduced 5-HIAA concentrations in animal experiments (Kreiss and Lucki, 1995) and among patients with major depression (Åsberg et al., 1977; Katz et al., 1994). Moreover, the observed positive correlation between CSF 5-HIAA and depression is in accordance with older concepts of serotonergic neurotransmission stimulating the behavior inhibition system (Gray, 1982; Cloninger 1987). In the study of Liljeberg et al. (1987), CSF MHPG concentrations were also relatively higher in depressed vs. non-depressed abstinent alcoholics. CSF MHPG was the only variable that was also correlated with anxiety, confirming the role of noradrenergic dysfunction in anxiety disorders (Charney and Heninger, 1986). A relative increase in CSF MHPG concentrations was also observed by Redmond et al. (1986) in depressed patients with increased anxiety and by George et al. (1990) among alcoholics with panic disorder.

In this group of alcoholics, as in most studies, depression decreased to mildly elevated levels during the first weeks of abstinence and seems to be secondary to chronic alcohol intake (Wagner Glenn and Parsons, 1991; Heinz et al., 1996). Stress hormone activation during detoxification (Iranmanesh et al., 1989; von Bardeleben et al., 1989; Heinz et al., 1995a) may affect mood states directly or indirectly via interference with serotonergic neurotransmission (Meltzer et al., 1994). It may not, however, on its own explain persistence of negative mood states after 4 weeks of abstinence, as cortisol concentrations had normalized at this time point (von Bardeleben et al., 1989; Heinz et al., 1995b; Adinoff et al., 1996b). This observation is interesting when the interaction with DHEA-S is considered. DHEA-S may modulate severity of depression by interacting with cortisol effects during early abstinence. As in other stress responses (Parker, 1989; Guazzo et al., 1996), DHEA-S concentrations may increase during physical detoxification stress with its activation of cortisol and norepinephrine release (von Bardeleben et al., 1989; Hawley et al., 1994). The rise in DHEA-S may help to reduce circulating cortisol levels (Wolkowitz et al., 1992) and might thus be involved in the termination of the physical stress response (Melchior and Ritzmann, 1994). This interpretation is supported by our observation of negative correlations between the ratio of DHEA-S to cortisol and the severity of depression. Depression might develop if DHEA-S release were inadequate relative to the activation of stress hormones during early abstinence. In accordance with this hypothesis, DHEA-S has been shown to relieve behavioral despair in an animal model of stress-induced depression (Reddy et al., 1998). A negative correlation between serum DHEA-S concentrations and severity of depression has been observed in clinical populations who suffered from stressful life events, such as spousal bereavement, severe physical disabilities, or functional limitations with poor life satisfaction (Legrain et al., 1995; Berr et al., 1996; Furuya et al., 1998). DHEA-S may thus

affect the development of depression in alcoholics who underwent stressful life events or suffered from detoxification stress during early abstinence.

We observed significant correlations between depression and DHEA-S but not DHEA concentrations, which may be due to the longer half-life and higher reliability of DHEA-S assessment or to different interactions of DHEA and DHEA-S with ethanol or stress effects (Melchior and Ritzmann, 1994; Baulieu, 1997). Both DHEA-S and DHEA have anxiolytic properties in the 'elevated plus maze test'; however, the anxiolytic effects of ethanol in this model were augmented by DHEA but blocked by DHEA-S (Melchior and Ritzmann, 1994). The anxiolytic effects of DHEA-S seem to be independent of its effects on $GABA_A$ receptor function (Imamura and Prasad, 1998); DHEA-S enhances long-term potentiation in the hippocampus (Randall et al., 1995) and increases central serotonin concentrations (Abadie et al., 1993). We did not observe a significant correlation between DHEA-S concentrations in blood, which are known to be associated with CSF DHEA-S concentrations (Guazzo et al., 1996), and CSF 5-HIAA concentrations. However, our data do not rule out a specific interaction between DHEA-S and serotonergic neurotransmission in certain brain areas such as the hypothalamus (Abadie et al., 1993).

In conclusion, severity of depression was associated with cortisol and DHEA-S concentrations and norepinephrine and serotonin metabolism during early abstinence. Given the importance of depression in determining the relapse risk of alcoholics (Hartka et al., 1991) on the one hand and the variability in neurosteroid plasma concentrations on the other (Orentreich et al., 1992), further studies with larger samples will be necessary to understand the potential role of the implicated variables in the pathogenesis of depression. The present results also raise the possibility that exogenous DHEA administration to depressed abstinent alcoholics may decrease depressive symptoms, as has been shown in other depressed populations (Bloch et al., 1999; Wolkowitz et al., 1999), but this, too, must await further study.

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